(2)

No. 06-922

IN THE
Supreme Court of the United States

NUTRACEUTICAL CORP.; SOLARAY, INC.,
Petitioners,

v.

ANDREW VON ESCHENBACH, COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION; U.S. FOOD AND DRUG ADMINISTRATION; MICHAEL O. LEAVITT, SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES; DEPARTMENT OF HEALTH AND HUMAN SERVICES; UNITED STATES OF AMERICA,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Tenth Circuit

BRIEF OF *AMICUS CURIAE* IN SUPPORT OF THE PETITION FOR A WRIT OF CERTIORARI

JOSEPH R. GUERRA*
I. SCOTT BASS
ROBERT A. PARKER
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, D.C. 20005
(202) 736-8000

Counsel for Amicus Curiae

* Counsel of Record

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BRIEF OF *AMICUS CURIAE*

The Natural Products Association ("NPA") respectfully submits this brief as *amicus curiae* in support of petitioner.[1]

INTEREST OF THE *AMICUS CURIAE*

The NPA is a trade association that represents over 10,000 manufacturers, wholesalers, distributors, and retailers of natural products, including dietary supplements. For over 70 years, the NPA (formerly known as the National Nutritional Foods Association) has advocated for the rights of consumers to have access to products that will maintain and improve their health, and for the rights of retailers and suppliers to sell these products. The NPA thus has a substantial interest in ensuring that government regulation of natural products, including dietary supplements, is not unduly burdensome, and that consumers are allowed to choose freely among natural foods and supplements that complement and improve their diets.

The question presented by this case is whether the Food and Drug Administration ("FDA") exceeded its authority by demanding that dietary supplements — which are classified as foods under the Dietary Supplement Health and Education Act of 1994 ("DSHEA"), Pub. L. No. 103-417, 108 Stat. 4325 — satisfy the stringent clinical risk-benefit analysis required for drugs. The FDA concluded that if dietary supplements do not satisfy that test, they may be deemed adulterated and banned. This standard is at odds with the DSHEA, and poses a significant threat to the NPA and its members. Unless the FDA's standard is reviewed, makers of dietary supplements

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[1] Pursuant to Rule 37, letters of consent from the parties have been filed with the Clerk of the Court. In accordance with Rule 37.6, *amicus* states that no counsel for either party has authored this brief in whole or in part, and no person or entity, other than *amicus*, has made a monetary contribution to the preparation or submission of this brief.

will be forced to incur much higher expenses in bringing their products to market, and consumers will pay higher costs as a result. Consumer choice will be curtailed, and the longstanding statutory distinction between drugs and dietary supplements (*i.e.*, foods), which Congress recognized and protected in the DSHEA, will be at an end. The NPA thus has a vital interest in the issue presented in this case, and files this brief in support of the petition for a writ of certiorari.

INTRODUCTION AND SUMMARY OF THE ARGUMENT

This case presents an exceptionally important issue of administrative and statutory law: may the FDA ignore the clear distinction Congress has drawn between drugs and dietary supplements, which are classified as foods, and thereby greatly expand its authority to declare a dietary supplement "adulterated"? Congress has given the FDA ample powers to protect public health and safety from adulterated foods, including dietary supplements. But in banning ephedrine alkaloids in dietary supplements, the FDA chose not to rely on its lawful powers. Instead, it took the opportunity to re-write the DSHEA, a statute the FDA strenuously, and unsuccessfully, opposed.

The FDA concluded that ephedrine alkaloids in dietary supplements pose an "unreasonable" risk to health, and are thus adulterated and should be banned. *Amicus* takes no position on whether, under the proper definition of "unreasonable," the FDA's decision was correct. The FDA relied, however, on an unauthorized "risk-benefit" analysis for dietary supplements, essentially requiring that dietary supplements provide significant health benefits, proved in rigorous clinical studies, sufficient to overcome any risks associated with the product. This is the standard that governs FDA pre-marketing approval of drugs; foods, including dietary supplements, are not subject to any such standard. The FDA's test, moreover, affords the agency an exceptionally large degree of discretion to ban dietary

supplements as "adulterated." Indeed, in applying the standard in this case, the FDA discounted the significance of most non-"health" benefits provided by dietary supplements — which are important to millions of consumers and are recognized expressly in the DSHEA — and concluded that those benefits would henceforth be insufficient to overcome even a small risk of harm. The District Court held that this expansive interpretation of the agency's powers violated the statute, but the Tenth Circuit reversed. The FDA's rule, and the Tenth Circuit's decision, cannot be reconciled with the DSHEA, and a writ of certiorari is warranted to bring the agency's rule in line with Congress's commands.

Unless this Court grants the petition for a writ of certiorari, the dietary supplement industry will suffer severe harm. A significant percentage of the principal makers of dietary supplements are located within the Tenth Circuit, and are therefore subject to its erroneous decision. If that decision is allowed to stand, the distinction between dietary supplements and drugs will effectively evaporate, the makers of supplements will be forced to conduct the types of rigorous clinical tests that Congress declined to require, and consumer choice in fulfilling their dietary needs (protected under the DSHEA) will be curtailed. *Amicus* urges the Court to grant the petition.

ARGUMENT

At the outset, *amicus* notes that it does not take a position on whether the end result of the FDA's erroneous analysis — the conclusion that no dose of ephedrine alkaloids in dietary supplements ("EDS") is safe, and that the product is therefore adulterated pursuant to 21 U.S.C. § 342(f)(1) — is correct. The FDA's consideration of this issue could, upon application of a proper standard, result in the banning of EDS. It is, however, unacceptable for the FDA to reach this result using a standard at odds with the governing statute, and *amicus* therefore urges this Court to grant a writ of certiorari to

clarify the proper standard by which the FDA (and the courts) are to judge whether dietary supplements are adulterated.

I. THE FDA'S RISK-BENEFIT STANDARD OBLITERATES THE LONGSTANDING STATUTORY DISTINCTION BETWEEN A "DRUG" AND A "FOOD", AND WARRANTS THIS COURT'S REVIEW.

A. Dietary supplements are regulated as foods, not drugs.

In 1994, Congress enacted the DSHEA to clarify that dietary supplements are foods, and are therefore exempt from regulation according to the strict standards applicable to drugs. See 21 U.S.C. § 321(ff).[2] Under the Food, Drug and Cosmetic Act of 1938 ("FDCA"), 52 Stat. 1040 (codified as amended at 21 U.S.C. § 301 *et seq.*), a "drug" is defined, *inter*

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[2] Section 321(ff) provides:

> The term "dietary supplement" –
>
> (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
>
> (A) a vitamin;
>
> (B) a mineral;
>
> (C) an herb or other botanical;
>
> (D) an amino acid;
>
> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
>
> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).
>
> * * *
>
> Except for purposes of [subsection (g) of this section], a dietary supplement shall be deemed a food within the meaning of this chapter.

alia, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1).

1. The statutory distinction between drugs and foods (including dietary supplements) is critical. The manufacturer of a drug must prove scientifically, to the FDA's satisfaction, that the drug is safe and effective before it is marketed. See 21 U.S.C. §§ 321(p), 355. This requires an explicit weighing of risks and benefits. See *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193, 203-04 (2005). In contrast, foods are presumed to be safe, and need not claim or prove any benefit whatsoever. See 21 U.S.C. § 342; *United States* v. *29 Cartons of *** an Article of Food*, 987 F.2d 33, 35 (1st Cir. 1993) ("Substances classified as 'food' are presumed safe."); S. Rep. No. 103-410, at 21 (Oct. 8, 1994) (noting that "a dietary supplement, as with any food, is presumed to be safe. It therefore may be lawfully marketed, unless and until the FDA, by a preponderance of the evidence, shows that the supplement is 'injurious to health.'").

This does not mean that makers of dietary supplements *cannot* claim benefits. Dietary supplements may include benefit claims related to the "structure or function" of humans, or that they prevent "classical nutrient deficiency disease[s]," or that they affect a person's "general well-being," provided that the maker has "substantiation" for the claim and the claim is "truthful and not misleading."[3] 21 U.S.C. § 343(r)(6). The makers of dietary supplements may not claim that their products "diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases," *id.*; any

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[3] The statement must also include a disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." 21 U.S.C. § 343(r)(6)(C).

such health claims will subject the supplement to regulation as a drug. 21 C.F.R. § 101.93(f). But nothing requires dietary supplement manufacturers to claim benefits at all, and even when they do, nothing in the statute requires that those claims be supported by the kind of rigorous clinical evidence used to prove the risks and benefits of drugs.

This regulatory distinction is rooted in the fundamental differences between dietary supplements and drugs: drugs are scientifically proven to have medicinal and therapeutic uses, while supplements (as the name suggests) enhance and complement a person's dietary intake of naturally occurring substances consumed as food. Drugs treat diseases that occur for reasons unrelated to the absence of the drug, while a supplement does not "treat" anything; rather, it remedies deficiencies of naturally occurring substances that are (or should be) part of our daily diet.

2. Prior to the enactment of the DSHEA, the FDA had ignored this distinction and attempted to subject dietary supplements to the clinical proof regime that governs drugs. It classified dietary supplements as "food additives," which are presumed to be unsafe and require the manufacturer to prove safety. See, e.g., *29 Cartons*, 987 F.2d at 35-36; *United States* v. *Two Plastic Drums, More or Less of an Article of Food*, 984 F.2d 814, 816-18 (7th Cir. 1993). Congress disapproved of this regulatory tactic. It expressly overrode the FDA's classification of dietary supplements by enacting § 321(ff), and harshly criticized the FDA's prior assertion of regulatory authority:

> Rather than meet its statutory burden, the FDA has chosen instead to treat dietary supplements as "food additives." . . . In the [C]ommittee's judgment, the FDA has disregarded the congressional intent underlying the law regulating food and food additives. That law plainly declares that a food may be sold unless the FDA finds that it is "injurious to health." In the

> absence of such evidence, the FDA has attempted to twist the statute in what the Committee sees as a result-oriented effort to impede the manufacture and sale of dietary supplements. We believe these "enforcement" actions discredit the agency and bring the law into disrepute, and has led to harassment and hardship for companies forced to defend themselves against this inappropriate regulatory strategy.

S. Rep. No. 103-410, at 21-22.

3. While it categorically rejected the FDA's attempt to subject dietary supplements to the clinical proof requirements that govern drugs, Congress did not leave the agency powerless to prevent harmful foods, including dietary supplements, from being marketed to consumers. To prevent the marketing of a dietary supplement (which is presumed safe, and need not confer a benefit), the FDA must prove that the supplement "presents a significant or unreasonable risk of illness or injury under (i) conditions of use recommended or suggested in labeling, or (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use . . . ." 21 U.S.C. § 342(f)(1)(A). The FDA "bear[s] the burden of proof on each element to show that a dietary supplement is adulterated." *Id.* § 342(f)(1). In keeping with the DSHEA's rejection of a "benefits" requirement for foods, the dietary supplement adulteration standard is concerned solely with "risk"; there is no mention of "benefits."

B. The risk-benefit test FDA uses to decide whether a dietary supplement is adulterated treats dietary supplements like drugs, which is precisely the harm to the industry Congress sought to alleviate in enacting the DSHEA.

In banning EDS in the face of highly publicized cases of adverse reactions apparently caused by the supplement, the

FDA trampled the distinction between drugs and foods and improperly applied the "risk-benefit" analysis that governs drug approval to conclude that EDS posed an "unreasonable risk of illness or injury." See FDA, *Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present An Unreasonable Risk*, 69 Fed. Reg. 6788, 6788 (Feb. 11, 2004) (hereinafter "Final Rule"). While *amicus* does not take a position regarding whether EDS is adulterated, it does take issue with the process by which the FDA reached that conclusion. The FDA's risk-benefit analysis is unwarranted and threatens to subject the makers of dietary supplements to the same plenary regulatory authority the FDA exercises over drug manufacturers, which is precisely the type of authority Congress denied the agency by enacting the DSHEA.

The Tenth Circuit concluded that the FDA's interpretation of the "significant or unreasonable" requirement of 21 U.S.C. § 342(f)(1)(A)(i) — *i.e.*, one authorizing the agency to conduct a comparative analysis of a dietary supplement's risks and benefits — was a permissible construction of the statute.[4] As explained in the petition for a writ of certiorari,

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[4] The Tenth Circuit relied on the principles of deference set forth in *Chevron U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), despite the fact the adulteration section of the DSHEA clearly states that a "court shall decide any issue under this paragraph on a de novo basis." 21 U.S.C. § 342(f)(1). *See Nutraceutical Corp.* v. *Von Eschenbach*, 459 F.3d 1033, 1037-38 (10th Cir. 2006). The Tenth Circuit concluded, without any support in the text of the statute or the legislative history, that the *de novo* standard was meant to apply only when courts "decide" matters under the statute, not when they "review" administrative decisions. *Id.* at 1037. The Court, citing an earlier Third Circuit decision, concluded that "'[h]ad Congress intended to supplant the well-established procedures for [Administrative Procedure Act] challenges [*i.e.*, deference], it would have been clearer about its objective.'" *Id.* (quoting *NVE, Inc.* v. *Dep't of Health & Human Servs.*, 436 F.3d 182, 194 (3d Cir. 2006)).

It is difficult to see, however, how Congress could have been clearer in stating that courts must "decide *any issue*" under the section using a *de*

this conclusion finds no support in the statute or the legislative history. *Amicus* believes it important to explain to the Court the adverse impact the FDA's rule will have on the dietary supplement industry.

1. As explained, dietary supplements are foods, and thus they are presumed safe and need not provide any articulated benefit (medicinal or otherwise) in order to be marketed. The FDA's reliance on a risk-benefit analysis in determining that EDS is unsafe destroys this distinction, and requires dietary supplements to have clinically verifiable health benefits sufficient to overcome any attendant risks — the same requirement that governs drug manufacturers.

The Tenth Circuit attempted to answer this concern by noting that the FDA has not required dietary supplement manufacturers to "provide data on the benefits of their products," and the FDA "has assumed its responsibility of gathering data, soliciting comments, and conducting the risk-benefit analysis." *Nutraceutical Corp.* v. *Von Eschenbach*, 459 F.3d 1033, 1039 (10th Cir. 2006). This does not, however, resolve the problem. The fact that the FDA bears the expense of proving the risks and lack of benefits in an

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novo standard. 21 U.S.C. § 342(f)(1) (emphasis added). As petitioners explain in their petition for a writ of certiorari, the Tenth Circuit has simply ignored Congress' express command and has instead manufactured an unsupported distinction between "deciding" cases and "reviewing" agency decisions as a way of justifying the FDA's risk-benefit analysis (which also has no support in the statute or the legislative history). This is incorrect and a writ of certiorari should be granted to review the Tenth Circuit's decision.

Even assuming the FDA is correct that EDS is adulterated, the FDA and the Tenth Circuit may not ignore Congress' statute to reach this result. *Amicus* submits that these decisions are precisely the sort of "result-oriented effort[s] to impede the manufacture and sale of dietary supplements" that led to the enactment of the DSHEA, efforts that Congress concluded "discredit the agency and bring the law into disrepute, and [lead] to harassment and hardship for companies forced to defend themselves against this inappropriate regulatory strategy." S. Rep. No. 103-410, at 22.

adulteration inquiry is irrelevant; the burden on industry (which the DSHEA sought to alleviate) is in subjecting dietary supplements to a benefit requirement that no other food is required to meet. The FDA's new-found condition that a dietary supplement's benefits outweigh its risks (upon pain of being deemed adulterated and hence banned) effectively forces the dietary supplement industry to undertake costly scientific studies to establish benefits of supplements before marketing them, if only to satisfy themselves that the product will withstand risk-benefit scrutiny by the FDA. That the FDA now requires dietary supplements to have scientifically verifiable benefits, whether established by industry or the agency, is plainly antithetical to the DSHEA's classification of dietary supplements as "foods."

Indeed, it appears that the only benefits in which the FDA is interested when conducting its adulteration inquiry are medicinal or therapeutic benefits related to disease — precisely the benefits dietary supplement manufacturers are not supposed to claim, lest they be reclassified as drugs. The FDA also requires that these benefits be proved by clinical scientific evidence, which is not required for any food, including dietary supplements, under the DSHEA or any other law — but is required for drugs.

In the Final Rule, the FDA dismissed most of the purported benefits of EDS, noting that "[t]he best *clinical* evidence for a benefit is for weight loss, but even there the evidence supports only a modest short-term weight loss, insufficient to positively affect cardiovascular risk factors or health conditions associated with being overweight or obese." Final Rule, 69 Fed. Reg. at 6825 (emphasis added). The FDA denied the relevance of "[o]ther possible benefits such as enhanced athletic performance, enhanced energy, or a feeling of alertness," *id.* (*i.e.*, claims related to "structure or function" and "general well-being," which are permitted by 21 U.S.C. 343(r)(6)) on the grounds that those benefits "lacked scientific

support" or are "trivial," Final Rule, 69 Fed. Reg. at 6825, and, in any event, "are temporary and do not improve health," *id.* at 6826.

Congress was fully aware, however, that dietary supplements, like other foods, may not "improve health," temporarily or otherwise, and that, if they do provide a benefit, it may be related to general well-being or the structure and function of the body. By classifying dietary supplements as foods, therefore, Congress did not tie the permissibility of selling supplements to any showing or evidence that they improve health. Moreover, in permitting the makers of dietary supplements to make certain types of health-related claims, Congress required only that such claims be "substantiated," not clinically proven. The FDA's "risk-benefit" analysis thus obliterates the distinctions between drugs and dietary supplements, and subjects the latter to requirements Congress plainly did not intend to impose.

2. The FDA's standard will inevitably force makers of dietary supplements to conduct rigorous clinical studies to establish the health benefits of their products. Producers must invest time and money in order to bring new dietary supplements to market. Under FDA's risk-benefit standard, however, any health risk, no matter how slight, justifies removal of a product unless there is clinical proof that the supplement "improve[s] health." Indeed, the FDA itself emphasized this:

> "Unreasonable risk[]" . . . represents a relative weighing of the product's known and reasonably likely risks against its known and reasonably likely benefits. In the absence of a sufficient benefit, the presence of even a *relatively small* risk of an important adverse health effect to a user may be unreasonable.

Final Rule, 69 Fed. Reg. at 6788 (emphasis added).[5]

In order to ensure that development and marketing investments will not be lost, therefore, producers will have to conduct expensive clinical tests proving substantial health benefits to provide some assurance that the FDA will not be in a position to ban supplements once they reach the market. This will present a barrier to market entry for small dietary supplement manufacturers and will necessarily lead to dramatic increases in the costs of supplements.[6] It will be especially damaging to the industry since dietary supplements, which are manufactured predominantly from natural food and plant sources, are no more patentable than

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[5] The Tenth Circuit accepted this argument, holding that the potential risk of a supplement "is more 'unreasonable' if the potential benefit is smaller." *Nutraceutical Corp.*, 459 F.3d at 1040. But the case the Tenth Circuit cited to support this interpretation of "unreasonable" risk – *Castrignano* v. *E.R. Squibb & Sons, Inc.*, 900 F.2d 455 (1st Cir. 1990) – involved a strict liability suit for harm caused by a *drug*. The jury instructions quoted in *Castrignano* (which the Tenth Circuit edited to replace the word "drug" with "product"), apply only to drugs subjected to the scientific risk-benefit analysis mandated by the FDCA:

> The product involved in this lawsuit is a drug. We all know that there is some danger in the use of any drug. Medical science is not yet developed to the point of perfection. Thus, in determining whether or not a drug is unreasonably dangerous, your emphasis should be on the term "unreasonable." In this determination you should consider the state of scientific and medical knowledge at the time the drug was manufactured; and you may strike a balance between the expected beneficial effects of the drug as opposed to its harmful effects, if any.

Id. at 459. Under the DSHEA, this standard does not apply to dietary supplements and other foods.

[6] The Tufts Center for the Study of Drug Development has estimated that the average costs of bringing a new drug to market, including the expensive clinical risk-benefit analysis required for FDA approval, approach $897 million. *See* FDA, *Greater Access to Generic Drugs*, *available at* http://www.fda.gov/Fdac/features/2003/503_drug.html.

apples, sugar, table salt, or milk. These are precisely the types of burdens Congress intended to eliminate when it enacted the DSHEA.

3. Many food products marketed by the dietary supplement industry on which consumers rely to supplement their diets are now at risk of being banned under this standard. Consider, for example, fiber. Fiber helps lower cholesterol, control diabetes, and prevent colon cancer. Fiber may also help with weight loss. Of course, fiber is a food, and the makers of fiber-rich foods and fiber supplements, though they have amply substantiated the benefits of a high-fiber diet, have not done so using the rigorous clinical risk-benefit analysis required of drugs. Millions of Americans consume fiber as part of their diet, in meals and as a supplement.

The benefits of fiber are dose dependent, with greater benefits at higher doses. High doses of fiber also carry risks, however. Some insoluble fibers bind other nutrients, including calcium, magnesium, phosphorous, and iron, which may lead to acute mineral depletion. Fiber may also cause less severe, but nonetheless significant, problems such as abdominal pain, diarrhea, and blockages of the gastrointestinal tract. Under the FDA's risk-benefit analysis, fiber (including fiber supplements) may be deemed adulterated at high doses because of these risks, unless a rigorous scientific process proves that fiber confers significant health and disease benefits sufficient to counterbalance those risks. Of course, as a food, fiber is not susceptible to such a process under DSHEA, but it is under the FDA's Final Rule.

Consider also fish oil, which contains the omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid). Dietary intake of fish oil from supplements or fishery products reduces triglyceride levels, lowers the risk of heart attack and stroke, slows the buildup of atherosclerotic plaques, and reduces blood pressure slightly. These claims have been substantiated, but, because fish oil is a food,

fisheries and makers of dietary supplements have not subjected those claims to the rigorous clinical risk-benefit analysis required of drugs. Many people rely on fish oil as part of their diet, in their meals and as a supplement.

As with fiber, the benefits of fish oil are dose-dependent, with greater benefits at higher doses. These higher doses carry risks, however. High doses of fish oil may increase the risk of bleeding, and increase a person's fat intake. Diets high in fat may increase cholesterol levels and the risk of heart disease and certain types of cancer. Fat has also been linked to weight gain and obesity. Again, under the FDA's risk-benefit analysis, fish oil may be declared adulterated at high doses because of these risks, unless a rigorous scientific process proves that fish oil, like a drug, confers significant health and disease benefits sufficient to counterbalance those risks. Of course, fish oil is a food, and should not be subjected to such a process, but the FDA's risk-benefit analysis treats foods like drugs nonetheless.

3. *Amicus* is, of course, aware that this Court ordinarily waits for more than one Circuit to decide an issue before granting a writ of certiorari. Here, however, such reserve is unnecessary. For historical and environmental reasons, over 150 dietary supplement manufacturers are located in Utah alone, accounting for up to 20% of the national market for supplements.[7] Indeed, dietary supplements are the third-largest industry in Utah, and many of the oldest and largest makers of dietary supplements are located in the state. Other major manufacturers are located elsewhere in the Tenth Circuit. Thus, the significant problems for the industry posed by the FDA's risk-benefit analysis, which the Tenth Circuit upheld (reversing the carefully considered opinion of the District Court), affect a substantial part of the dietary

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[7] *See* Econ. Devel. Corp. of Utah, *Nutritional Prods. Indus. Profile* 1 (2005), *available at* http://www.edcutah.org/datacenter/publications/documents/NutritionalProducts082305_000.pdf.

supplement industry. Unless this Court grants the petition for a writ of certiorari, the Tenth Circuit's decision will be the final word for the industry, and will effectively unravel the DSHEA.

II. THE FDA'S RISK-BENEFIT STANDARD IS UNNECESSARY.

The FDA did not have to rely on a risk-benefit analysis to give meaning to the term "unreasonable" in 21 U.S.C. § 342(f)(1)(A). The Tenth Circuit faulted the District Court for "conflating the terms 'significant' and 'unreasonable,' thereby rendering 'unreasonable' superfluous," and concluded that "[t]he use of 'unreasonable' to qualify risk in addition to 'significant' makes it clear that Congress intended to integrate a risk-benefit analysis in the former." *Nutraceutical Corp.*, 459 F.3d at 1040. But the Tenth Circuit's conclusion that a risk-benefit analysis is necessary to avoid statutory redundancy is mistaken, and cannot justify an interpretation that ignores the clear distinction Congress drew between dietary supplements and drugs, and imposes precisely the type of burdensome regulation that Congress refused to impose on the dietary supplement industry.

The Tenth Circuit asserted, without any supporting citation, that the "plain meaning of a 'significant risk' is a great danger." *Nutraceutical Corp.*, 459 F.3d at 1040. But a risk is a "possibility of loss, injury, disadvantage, or destruction," and a principal definition of "significant" is "having or likely to have influence or effect." *Webster's Third New Int'l Dictionary* 1961, 2116 (1993). Thus, a "significant risk" is a possibility of injury that is likely to have a deleterious influence or effect, *i.e.*, a statistically likely injury or harm. See also *id.* at 2116 (defining "significance" as "the quality of being statistically significant"). Contrary to the Tenth Circuit's belief, therefore, a harm need not be "great" or grave to be "significant." Rather, if consumption of a dietary supplement at the recommended or ordinary dose is statistically likely to cause diarrhea, nausea, or headache, it

presents a "significant risk" of "illness" even though none of these illnesses is grave or great.

By contrast, in the context of dietary supplements, "unreasonable" does refer to more grave dangers or harms. "Unreasonable" is defined as "exceeding the bounds of reason or moderation: inordinate, unconscionable." *Webster's Third New Int'l Dictionary* at 2507; see also *Black's Law Dictionary* 1537 (7th ed. 1999) (defining "unreasonable" as "[n]ot guided by reason; irrational or capricious," and explaining that an "unreasonable decision" in the administrative context is "so obviously wrong that there can be no difference of opinion among reasonable minds about its erroneous nature"). These definitions do not require a weighing of benefits and risks. Rather, because *all* supplements are meant to enhance and complement a healthy diet, *no* reasonable person would risk death (or a comparably serious injury) to take a supplement, even if the risk of such a grave harm is relatively slight. Thus, even a statistically small chance that a dietary supplement could lead to death, paralysis, or blindness would be sufficient to show that a dietary supplement presents an "unreasonable risk" of "illness or injury," without any need for balancing the clinically proven benefits of the supplement. By contrast, it might be entirely reasonable to consume a drug that poses the same small chance of such harms, because drugs, unlike foods, are intended to treat or cure illness and disease. Thus, it would not be "unreasonable" to take a drug that poses a slight risk of death, particularly if it treats a disease that is already life-threatening.[8] See, e.g., *Merck KGaA*, 545 U.S. at 204 (explaining that the FDA "might allow clinical testing of a

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[8] A supplement like EDS, for example, might well pose an "unreasonable" risk under this standard since a reasonable person would be expected to know that it may result in death. Regardless of the benefits EDS provides, *no* dietary supplement (*i.e.*, a food) could justify such a risk, whereas a drug might – hence the use of risk-benefit analysis to evaluate whether a drug is safe, effective, and marketable.

drug that posed significant safety concerns if the drug had a sufficiently positive potential to address a serious disease, although the agency would not accept similar risks for a drug that was less likely to succeed or that would treat a less serious medical condition" (internal quotation marks omitted)).

Regardless of what "unreasonable" may mean with respect to drugs (which are subject to express risk-benefit requirements), "substantial" and "unreasonable" identify two different categories of harm in the context of dietary supplements: the first, a relatively high likelihood of any harm, no matter how minor the harm itself; the second, a relatively severe harm, no matter how slight the chance of occurrence. These definitions give meaning to both terms, and are consistent with the DSHEA's classification of supplements as foods, which do not need to provide a benefit (let alone a clinically proven health benefit) to be marketable. There is thus no reason to think, as the Tenth Circuit did, that removing benefits from the equation renders one of the terms superfluous. Since the FDA's rule requires dietary supplements to provide substantial health benefits if they carry some risk, it runs afoul of Congress' express commands in the DSHEA.

CONCLUSION

For the foregoing reasons, *amicus curiae* respectfully urges this Court to grant the petition for a writ of certiorari to allow the petitioner and other interested parties (including *amicus*) an opportunity to prove, on the merits, that the FDA has overreached and exceeded the bounds of Congress' statutory scheme.

Respectfully submitted,

JOSEPH R. GUERRA*
I. SCOTT BASS
ROBERT A. PARKER
SIDLEY AUSTIN LLP
1501 K Street, N.W.
Washington, D.C. 20005
(202) 736-8000

Counsel for Amicus Curiae

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* Counsel of Record